demonstrating these parameters, that there is a neointima incorporating all stent struts, minimal fibrin, minimal long-term inflammation, and a rapidly endothelialized lumen, consistent with vessel healing.

We have also been very interested in understanding the endothelial cell response to a XIENCE V system. As such, we have conducted several novel research studies in collaboration with Dr. Renu Virmani in order to understand the endothelial cell response to a XIENCE V stent in comparison to a metallic VISION stent as well as other commercially available drug-eluting stents.

All of these studies were conducted in a rabbit model, which allows us to really differentiate the endothelial response to various stent platforms.

And as part of these studies, we conducted an assessment, an in-depth assessment, of the endothelial cell coverage by qualitative and quantitative means through

scanning electron micrograph evaluation. We also looked for the presence of specific endothelial cell markers through both confocal microscopy and molecular evaluation.

This I chose representative scanning electron micrograph of the lumenal surface of stents that have been cut longitudinally following 14 days in a rapid vessel, iliac vessel.

And, as you can see, if we look at the XIENCE V, we have good endothelial cell coverage of the stent surface. And it's somewhat similar in coverage as the VISION metallic stent. And there is greater coverage as compared to the other commercially available drug-eluting stents.

We quantified the endothelial cell coverage. And the data is demonstrated here. And in order to assess coverage, we looked both above the stent struts as well as in between stent struts.

And when we look over the stent

struts, you can see that there is significantly greater coverage with the XIENCE V stent as compared to other commercially available drug-eluting stents. And the XIENCE V stent has similar coverage to a VISION metallic stent.

In order to understand endothelial cell integrity and functionality, we looked for the presence of two specific biomarkers. We looked for expression of platelet endothelial cell adhesion molecule, which is a membrane glycoprotein that is constitutively expressed by endothelial cells. And we also looked for production of vascular endothelial growth factor, which we believe should be down-regulated with complete endothelialization.

The expression of PECAM is demonstrated here. This was evaluated by immunohistochemical means. And the chemical expression is shown here. And, consistent with the endothelial data that I just showed,

there is significantly greater expression of PECAM on the part of XIENCE as compared to other drug-eluting stents.

In terms of VEGF production, we looked for both protein levels as well as gene expression. And the data shown here are from two different sets of experiments. And the data is consistent with one another.

We do see that the levels of VEGF expression for XIENCE are similar to a VISION metallic stent and less than the other drug-eluting stents. And we believe this is consistent with endothelialization.

So, to summarize, XIENCE V demonstrated rapid re-endothelialization compared to other drug-eluting stents. And XIENCE V demonstrated enhanced endothelial cell function. And, to conclude, we do believe that rapid endothelial cell coverage and function are consistent with vessel healing.

I would now like to introduce Dr.

Gregg Stone, who will speak to you about the SPIRIT clinical program.

DR. STONE: Thank you, Leslie.

Good morning. My name is Gregg Stone. I'm an interventional cardiologist at Columbia University Medical Center. And I am here to discuss the preclinical investigational pathway that has been undertaken for the SPIRIT program of the XIENCE V stent.

I have also represented in the past Boston Scientific as the principal investigator of the pivotal TAXUS IV trial that led to approval of that device in the United States and have also been the principal investigator of the United States TAXUS 5 and TAXUS 5 ISR trials.

I currently receive research support from both Abbott Vascular and from Boston Scientific, which are the manufacturers of the two stents that I will be discussing in this presentation and which were pitted

against each other in the SPIRIT II and SPIRIT III trials. And I also do work with other device companies that manufacture devices that I won't be discussing today.

This is the second time of four you are going to see this slide describing the 16,000 patients that will be enrolled, have been rolled, and will be enrolled in the pre-approval and the ongoing and planned clinical studies for the XIENCE V stent.

And I am going to be specifically describing the results of four different studies. These of these were randomized trials: the SPIRIT FIRST trial, the SPIRIT II, and SPIRIT III, and then the SPIRIT III 4.0-millimeter stent registry arm, which was part of the SPIRIT III randomized trial.

So if we first look at the SPIRIT FIRST trial, this was the first in-human use of the XIENCE V stent. This trial was performed at a time when one could still compare a drug-eluting stent versus a bare

metal stent. And this compared the XIENCE V stent versus the otherwise similar bare metal VISION stent.

This was a relatively simple randomized controlled trial in single de novo lesions. It was performed in 60 patients in 9 sites in Europe. Again, relatively short focal lesions with a reference vessel diameter of three millimeters and a lesion length of up to 12 millimeters were enrolled in this study and then randomized one to one to either the XIENCE V Everolimus-Eluting Stent versus an otherwise identical multi-length VISION bare metal stent.

Again, this was prospective. This was single blind and randomized. Angiographic and intravascular ultrasound was performed or intended to be performed at six months and one year in all patients with clinical follow-up performed at regular intervals up to five years.

I will be emphasizing the primary

and the major secondary endpoints for these studies. The primary endpoint was angiographic in-stent late loss at 180 days, with a major secondary endpoint of intravascular ultrasound-determined percent volume obstruction; that is, tissue growth within the stent.

At 180 days, this trial, of course, was underpowered to look at clinical events. Both of these endpoints looking at the degree of neointimal growth within the stents over time were powered for superiority. That is, the XIENCE V stent had to be better than the bare metal stent. And the principal investigator was Patrick Serruys from the Thorax Center.

What I will be doing for all of the data that I will be showing is I will be only showing you p-values when it was either a primary endpoint or a powered secondary endpoint. Otherwise we will be displaying the results as either differences or relative

risks with confidence intervals, which should be considered secondary analyses or exploratory.

Here you can see the primary endpoint of this trial, SPIRIT FIRST drug-eluting stent, versus bare metal stent looking at in-stent late loss. That is, from the time of the immediate post-procedure to six months later, how much tissue actually accumulated at the worst spot within the stent as determined by quantitative coronary angiography?

And you can see there was a marked reduction in the amount of late loss from a mean of 0.85 millimeters with the VISION bare metal stent to 0.1 millimeter with the XIENCE V stent, an 88 percent reduction, which was highly statistically significant.

When one looks at the major secondary endpoint of percent volume obstruction, this now looks with a more sensitive intravascular ultrasound method,

looking at the percentage of tissue growth now on a volumetric basis within the stent margins that were occluding the illumene, if you will.

You can see that, similarly, there was a marked reduction in the percent volume obstruction from almost 30 percent of the stent being filled with tissue with the VISION bare metal stent. And this was reduced 72 percent to an 8 percent volume obstruction with the XIENCE V stent, again highly statistically significant.

Now, I did mention that this trial was underpowered for clinical events, but, of course, these patients were followed clinically. And we have data now out to three years on the patients that were enrolled in the XIENCE V stent versus the VISION stent in SPIRIT FIRST.

You can see that, importantly, there were no cardiac deaths in either arm. Other events were relatively low in frequency, especially in the XIENCE V arm, in these

patients followed out to three years.

I will point out that there were trends towards reduced target lesion revascularization. This is the purest clinical surrogate of drug-eluting stent efficacy. This means ischemia leading to a repeat procedure due to restenosis, either at the lesion itself or at the margins out five millimeters from the lesion; the composite endpoints of major adverse cardiovascular events, which I will describe further later; and target vessel failure, also tended to be reduced with the XIENCE V stent, but, again, we weren't powered to show differences for this trial. And, perhaps most importantly, there were no cases of stent thrombosis out to three years in this small study with either the XIENCE V stent or the VISION bare metal stent.

So the conclusions from the SPIRIT FIRST trial were that this trial met both its pre-specified primary and major secondary

endpoints, demonstrating superiority of the XIENCE V stent compared to the bare metal multi-link VISION stent in reducing late loss and percent volume obstruction.

We now entered a phase in clinical development where most physicians were using drug-eluting stents for the majority of patients with coronary artery disease. And it no longer became feasible to compare drug-eluting stents to bare metal stents.

So now we will be looking at studies comparing the XIENCE V stent to the otherwise widely utilized paclitaxel-eluting TAXUS stent. So this is DES versus DES. And the first such study, which was designed in Europe, was the SPIRIT II randomized controlled trial.

This was a more challenging study in which high-risk patients were enrolled. Patients were enrolled with up to two de novo lesions, rather than one, with a maximum of one lesion per epicardial vessel. And the

lesions were also more challenging. They could be in smaller vessels or larger vessels, ranging from 2.5 to 4.25 millimeters and, probably even more importantly, much longer, up to 28 millimeters in length.

A total of 300 patients were enrolled in this trial at 28 sites outside the United States. And patients were randomized three to one to either the XIENCE V Everolimus-Eluting Stent or the TAXUS Paclitaxel-Eluting Stent. So this was also a prospective, single-blind, randomized trial.

Angiographic and intravascular ultrasound follow-up was performed or intended to be performed at 180 days in all patients and 2 years in approximately half the patients. Clinical follow-up was performed at regular intervals up to five years.

Now, the primary endpoint for this 300-patient trial, in which a DES was compared to a DES, was angiographic in-stent late loss at 180 days. And this trial was powered to

demonstrate the XIENCE V compared to TAXUS was first not inferior and then if it met that endpoint to test whether or not it was superior in terms of reducing in-stent late loss.

The powered secondary endpoint was angiographic in-segment late loss at 180 days. And this was powered for non-inferiority. And Patrick Serruys at the Thorax Center was again the principal investigator.

This shows now for the first primary endpoint the angiographic patient flow at 6 months of 300 randomized patients. Six-month angiographic follow-up was completed in 92 percent. And Europe is very good with angiographic follow-up.

And if we look at the primary endpoint of in-stent late loss, one can see that not only was the XIENCE V stent shown to be non-inferior to the TAXUS stent in terms of late loss, but it was also highly statistically superior with a marked 69

percent reduction in late loss, from 0.36 millimeters with TAXUS to 0.11 millimeters with XIENCE V.

And I will just remind you this compares to 0.8 to 1 millimeters with bare metal stents. So this expanded scale, you still see this marked reduction in late loss with XIENCE V compared to the otherwise leading TAXUS stent.

When one looks at in-segment late loss, this now looks not only at the biologic efficacy of the drug-eluting stent device; that is, what is going on within the margins of the stent; that is, in-stent late loss, but also takes into account the five-millimeter edges. And this can look at balloon stent mismatch issues, drug diffusion effects, and other such effects. And this is more the whole lesion itself.

And you can see even considering in-segment late loss, while the trial was only powered for non-inferiority, you can see there

tended to be a 53 percent reduction in in-segment late loss, from 0.15 millimeters with TAXUS to 0.7 millimeters with the XIENCE V stent.

Looking at the intravascular ultrasound measures, again, of percent volume obstruction, this is the most commonly relied upon IVUS measure. You can see that there is a statistically significant 66 percent reduction in volume obstruction from 7.4 percent with TAXUS -- and, again, this usually compares to about 30 percent with the bare metal stent -- down to 2.5 percent with the XIENCE V stent. So the DES is doing what it is supposed to be doing in terms of inhibiting tissue regrowth.

Now, if we look at the clinical outcomes, at one year -- and this trial, again, was not powered for clinical endpoints, but, of course, it's important to look at how the patients did -- you can see the 12-month clinical follow-up, which is the data that we

currently have from this trial and has been completed in 99.3 percent of the patients.

First, looking at safety endpoints, stent thrombosis has been adjudicated by both the pre-specified per-protocol definition and then by now the widely used Academic Research Consortium definitions; that is, definite or probable ARC stent thrombosis. And one can see that the rates of stent thrombosis out to one year were low with the TAXUS stent -- that's the red -- and also very low with the XIENCE V stent.

If one looks at cardiac death, there was zero percent cardiac death at one year with the XIENCE V stent versus 1.3 percent with the TAXUS stent. There was a numerical trend towards less myocardial infarctions with XIENCE V compared to TAXUS. And there was a borderline statistically significant reduction in target lesion revascularization.

Again, this is clinical restenosis.

These are real procedures due to recurrent ischemia, recurrent angina, recurrent symptoms requiring rehospitalization for repeat either angioplasty or surgery. So 6.6 percent with TAXUS and 1.8 percent with XIENCE.

As a result, when we start looking at composite measures of safety and efficacy -- and I am not a big fan of these composite measures because you can obviously have the components going different directions. So it's important to look at the components.

But the first composite measure that we often look at is MACE. And this is cardiac death, myocardial infarction, or target lesion revascularization which is relatively specific to the stent itself.

And here you can see that for the first time in a randomized trial, we actually saw a significant reduction in MACE with one drug-eluting stent versus another from 9.2 percent, which is a relatively low number, actually, with the TAXUS stent for this type

of lesion and patient mixed, but reduced to 2.7 percent with the XIENCE V stent.

Now, the next component that we can look at of what can happen in terms of repeat vascularization is what we call target vessel revascularization remote; that is, remote from the target lesion. This could be new lesions that occur in the side branches, from guide catheter trauma, from a new distal lesion, progression of disease.

We wouldn't expect a drug-eluting stent to either prevent this or to improve upon it. And you can see these two drug-eluting stents had similar rates of TVR remote.

So if we look at the second composite measure of target vessel failure, which is somewhat more of a general measure now looking at cardiac death, MI, TLR, or TVR remote. You can see, of course, this will always dilute out a little bit of the ability to see the difference between two devices.

And that's what we see here.

Nonetheless, you could see a trend towards a 51 percent reduction in target vessel failure with XIENCE compared to TAXUS, 9.2 versus 4.5 percent.

Thus, the conclusions from SPIRIT II are that the SPIRIT II trial met its pre-specified primary endpoint, demonstrating superiority of the XIENCE V stent compared to the TAXUS stent in reducing in-stent angiographic late loss.

So this brings us now to the pivotal United States-based SPIRIT III randomized controlled trial, which was designed in concert with FDA to support this pre-market approval application of the XIENCE V stent versus the TAXUS stent, again DES versus DES. And, as you'll see, this trial was designed in very similar fashion to SPIRIT II.

So, once again, we took patients with up to two de novo lesions with a maximum

of one lesion per epicardial vessel, with very similar reference vessel diameters and lesion lengths, as in SPIRIT II, an RVD of 2.5 to 3.75 millimeters and lesion lengths up to 28 millimeters. This actually matches the labeling of the TAXUS stent for use in the United States.

And this was a much larger study, randomizing 1,002 patients at 65 United States sites. Patients were randomized two to one to the XIENCE V stent compared to the TAXUS stent.

This again was a prospective single-blind, randomized trial. Angiographic and intravascular ultrasound was performed at eight months in pre-specified subsets of patients. And I'll describe this for you coming up.

Clinical follow-up was intended to five years at regular intervals in all patients. And that's ongoing. The primary endpoint for this trial was angiographic

in-segment late loss at eight months. So we have now extended from in-stent late loss, which is easier to show because that's just looking at big differences within the stent, to now in-segment late loss, which is a more comprehensive measure taking into account what goes on at the edges, where the drugs might not be able to get to.

So, looking at this more comprehensive measure at eight months and this trial is powered, again, for sequential non-inferiority and superiority testing of XIENCE V versus TAXUS.

The first 564 patients enrolled into this trial were entered into the angiographic follow-up cohort with the patients after that enrolled in a non-angiographic follow-up cohort. There were no statistically significant differences in the baseline characteristics of the patients intended for angiographic follow-up versus those who weren't.

Now, the major secondary endpoint, which was actually also a co-primary endpoint because both endpoints were required to be met for regulatory approval, was the first time we have actually looked at a clinical endpoint. And that was ischemia-driven target vessel failure.

So this is this general measure of safety and efficacy at nine months, cardiac death, myocardial infarction, or target vessel revascularization that consists of target lesion or vascularization or TVR remote.

With 1,002 patients, this trial is powered for non-inferiority. And that was the regulatory burden that had to be met. The trial was not powered for superiority for target vessel failure. And it was my honor to be involved as the principal investigator of this study.

Now, in addition, we also wanted to look at the safety and efficacy of a 4.0-millimeter stent. And we often treat

large vessels with drug-eluting stents. Right now we have to take the currently available 3.5-millimeter stents, put them in, expand them with a larger balloon to get them up to 4.0. There is not currently an approved four-millimeter drug-eluting stent on the United States market.

So what was worked out in concert with FDA to evaluate this since we couldn't randomize it to another 4-millimeter drug-eluting stent was to take within these patient populations the appropriate lesions that were eligible for a 4-millimeter stent -- and that's a reference vessel diameter of 3.75 to 4.25 millimeters -- and to do a small registry, basically just to see if the results were consistent with the XIENCE V stent and at least not inferior to the results of the TAXUS stent in the remainder of the randomized SPIRIT III trial.

So this was a prospective single-blind 4.0-millimeter registry compared

to the concurrent TAXUS control arm from SPIRIT III with angiographic follow-up at 8 months in all patients intended with clinical follow-up ongoing to 5 years. And the primary endpoint that was agreed upon for regulatory approval was angiographic in-segment late loss at eight months powered for non-inferiority to TAXUS from SPIRIT III.

So if we first look at these primary angiographic endpoints, this is the randomized trial, the first 564 patients. And you can see that at 8 months, angiographic follow-up was completed in 77 percent of patients.

Usually in the United States, we get about 75 to 80 percent. And, in fact, we have powered this trial for 75 percent angiographic follow-up. If one extends this out to another one month, then we are up to 82 percent angiographic follow-up, but this is the official formal window, with 77 percent.

This was the primary endpoint of

SPIRIT III in-segment late loss at eight months. And, once again, one can see that not only was the XIENCE V stent compared to the TAXUS stent -- not only did it meet the primary endpoint of non-inferiority, but it was also highly statistically significant superior in terms of reducing in-segment late loss across the entire lesion and at the edges from 0.28 millimeters with TAXUS to 0.14 millimeter with XIENCE V, a 50 percent reduction p-value of 0.004.

When one looks at the four-millimeter stent, you can see that, again, the late loss was 0.17 millimeters with this, which was shown statistically to be non-inferior to the 0.28 millimeters to the TAXUS randomized control trial. You can look, however, at the confidence intervals of the difference. And you can see that it does not overlap unity. So this actually was a reduction.

Now, if we go back to the

randomized control trial and first look at IVUS measures, we can see the IVUS once again supports on a volumetric basis what we saw on a spot analysis with the angiogram. And that is first looking at a slightly different endpoint of neointimal hyperplasia volume.

This is the amount of tissue that grows within the stent margin over the eight-month follow-up period. You could see that 21-millimeter3 of tissue on average grew within the TAXUS stent versus 10.1-millimeter3 in the XIENCE V stent, a statistically significant 52 percent reduction. And if one looks at, again, percent volume obstruction, you can see similar types of findings, a 38 percent reduction, from 11.2 percent down to approximately 7 percent, with TAXUS versus XIENCE, respectively.

Now, importantly, intravascular ultrasound is a very powerful tool that allows us not to look at only the tissue inside the stent but to look at abnormal vascular

responses. And what we like to see with a drug-eluting stent is that it inhibits tissue growth but doesn't do anything abnormal to the vessel wall. By angiography, we didn't see any aneurysms or ectasia in the study, but ultrasound is more sensitive than that.

What we can do is look at the external elastic lamina volume. This is actually the size of the entire vessel by intravascular ultrasound. And what one can see is when one looks at the XIENCE V stent patients in media after implant to eight-month follow-up by ultrasound, you can see that there is no growth in the vessel. It basically stays where you left it.

When one looked at the TAXUS stent, we see what we have seen in other trials. And that is an expansion or positive remodeling of the vessel. So the stent doesn't change, of course, over time, but the vessel actually is positive remodeling or expanding outward.

And when we want to see after this

how this translates into the most concern that we have of incomplete stent apposition, which is acquired during follow-up -- that means a stent that was well-implanted initially at the end of the procedure but the artery, which presumably from vascular toxicity is positive remodeling, so it pulls away from the stent. This is a concern that, at least anecdotally, has been related to stent thrombosis.

We can see that with both stents, this was actually quite low. It occurred in 1.1 percent of XIENCE V patients and 2.3 percent of TAXUS patients. So what we have seen here by looking at angiography and what is supported by IVUS is a stent that leads to larger lumens compared to the other drug-eluting stent without positive remodeling; that is, without vascular toxicity, and without a risk of late acquired incomplete apposition.

Now let's look at the clinical follow-up in SPIRIT III of the 1,002

randomized trials. Nine-month follow-up was completed in about 98 percent of patients and 12-month follow-up in approximately 97.4 percent of patients. And this was the co-primary endpoint of the trial; that is, target vessel failure at nine months.

Again, this was powered for non-inferiority. And the XIENCE V stent was shown to be non-inferior to the TAXUS stent for the co-primary endpoint, the first time a clinical endpoint has been pre-specified, target vessel failure from 9.7 percent with TAXUS to 7.6 percent with XIENCE V, a relative risk reduction of 21 percent, but you can see the confidence interval does cross the line of unity, so not statistically significant from superiority testing.

We now have follow-up to all of the patients out to one year in the SPIRIT III trial. And these are the hazard curves. Again, we have got TAXUS in red and XIENCE V in blue.

You can see here that there tends to be less target vessel failure in the XIENCE V arm compared to the TAXUS arm, 11.1 percent versus 8.5 percent, a relative 25 percent difference, but the p-value is .8. But this trend -- and I will get back to this -- is due to what tends to be less peri-procedural non-Q-wave myocardial infarctions very early on, with then what tends to be a little bit less ischemic target lesion revascularization later on.

This comes out, actually, more so when one now looks at the more stent-specific composite endpoint of major adverse cardiovascular events. Again, this is cardiac death, myocardial infarction, or target lesion revascularization that is right at the site of the stent and at the edges of the stent.

Here you can see the difference again in peri-procedural non-Q-wave MIs. And then you do see the curve spread over time, as I will show you later, because of less target